REMARKS

A Reply and Amendment under 37 C.F.R. §§ 1.112 and 1.121 was submitted on August 4, 2005, in response to the Office Action dated February 4, 2005. Applicants hereby submit a Supplemental Reply and Amendment and respectfully request reconsideration of the present application in view of the above amendments and the following remarks. In the Reply and Amendment submitted August 4, 2005, Applicants amended claim 1 and cancelled claims 7-17 without acquiescence to any rejection and without prejudice to filing a related divisional, continuation, or continuation-in part application. In this Supplemental Reply and Amendment, Applicants have amended claim 1 that was set forth in the Reply and Amendment submitted August 4, 2005, and have added new claims 22-23 to define more clearly certain subject matter encompassed by Applicants' invention. These amendments are made without acquiescence to any rejection and without prejudice to filing a related divisional, continuation, or continuation-in part application. Support for the amended claim and new claims can be found throughout the specification, for example, at page 13, lines 10-28; page 17, lines 12-14; page 35, lines 9-18; page 39, lines 4-12; page 39, line 23 through page 40, line 1; page 42, lines 14-22; page 45, lines 3-18; page 61, lines 5-19; page 63, lines 21-24; Table 4; Figure 2, and Figure 7. No new matter has been added. Accordingly, upon entry of this amendment, claims 1, 2, and 18-23 are currently pending.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH (WRITTEN DESCRIPTION)

In the Office Action dated February 4, 2005, claims 1, 2, and 7-21 are rejected under 35 U.S.C. § 112, first paragraph, for allegedly being directed to subject matter that is not adequately described in the specification. Specifically, the Action alleges that the specification does not describe a genus of seven surface markers selected from the recited group of antigens that would be useful for identifying a type of leukemia in a human subject.

Applicants respectfully traverse this rejection and submit that the specification reasonably conveys to a person skilled in the art that Applicants possessed the claimed invention at the time the application was filed. Applicants respectfully submit that rejection of claims 7-17

is rendered moot by the amendments submitted herewith, which include cancellation of these claims without prejudice.

The present claims are directed to methods for identifying a leukemia of T cell, B cell, or myeloid lineage in a subject (*e.g.,* a human or non-human animal). The method comprises (1) contacting a biological sample that comprises leukocytes from the subject with an array of immunoglobulin molecules immobilized to a solid support, wherein the immunoglobulin molecules are specific for cell surface marker antigens, wherein the cell surface marker antigens comprise at least seven cell surface marker antigens selected from the list in Table 4, and wherein the cell surface marker antigens distinguish leukemias of T cell, B cell, or myeloid lineage; and (2) determining which cell surface marker antigens have bound to which immobilized immunoglobulin molecules to establish a differential pattern of density of binding that identifies a leukemia that is of T cell, B cell, or myeloid lineage.

The specification describes a method for identifying and distinguishing different types of leukemias that are of T cell, B cell, or myeloid lineage (*see, e.g.,* specification, at page 42, lines 14-22; page 44, line 24 through page 45, line 18; page 61, lines 5-19; Table 4; Figures 5 and 7) in a biological sample that contains leukocytes, which express cell surface marker antigens (*see, e.g.,* specification, page 45, lines 3-18; page 17, lines 12-14, and Figure 2). The sample comprising leukocytes is contacted with an array of immunoglobulin molecules, which are immobilized to a solid support and which are specific for cell surface marker antigens that distinguish leukemias of T cell, B cell, or myeloid lineage (*see, e.g.,* page 35, lines 15-18; page 61, lines 5-19; Table 4; page 17, lines 12-14 and Figure 2). Binding of each immunoglobulin of the array to a cognate cell surface antigen expressed by the leukocytes is then determined, thus providing a differential pattern of density that is characteristic of a leukemia that is of T cell, B cell, or myeloid lineage (*see, e.g.,* specification, page 26, lines 11-20; page 39, lines 4-12; page 39, line 23 through page 40, line 1; page 42, lines 14-22; page 61, lines 5-19; page 63, lines 21-24; Table 4; Figures 5 and 7; *see also, e.g.,* page 27, lines 4-18 and page 34, lies 12-16).

The specification illustrates that a differential pattern of density is the relative density of interaction between the antibodies and the cell surface antigens, and which provide a pattern of expression that can be visualized as an image (see Figures 5 and 7) and/or quantified

(for example, quantified according to a scale (-; +/-; +; ++; +++; ++++)) (*see, e.g.*, specification, page 26, lines 11-20; page 47, lines 15-22; page 61, lines 5-19; Table 4; Figure 5; Figure 7). The differential patterns of density provide recognizable patterns for different leukemias, which are exemplified in Table 4 and Figure 7 (*see, e.g.*, specification, at page 45, lines 3-9). Thus, the claimed method identifies and distinguishes a leukemia of T cell lineage (as represented, for example, by CCRF-CEM T cell leukemia (*see, e.g.*, page 61, lines 1-19; Table 4; Figure 7b)), a leukemia of B cell lineage (as represented, for example, by Raji B cell lymphoma (*see, e.g.*, page 61, lines 1-19; Table 4; Figure 7c)), and a leukemia of myeloid lineage (*see, e.g.*, page 61, lines 1-19; Table 4; Figure 7d)).

In addition, the Action asserts that "[w]hile the specification contemplates arrays that minimally contain 7 antibodies, the specification contains no examples of sets of 7 antibodies that would be useful for performing the claimed methods, and specifically would result in the establishment of a discriminatory image of antigen expression and which is characteristic of a type of leukemia" (Office Action dated February 4, 2005, page 7, second paragraph). However, the Action is not only incorrect on this point substantively (see, for example, page 61, lines 1-20) but misconstrues the present invention. The presently claimed embodiment is directed to methods for identifying a leukemia by using the binding interaction between immunoglobulin molecules and their cognate cell surface marker antigens to create a discriminatory image. This image and image pattern are the truly interesting and dramatic features.

Furthermore, the Examples and tables demonstrate that many cell surface marker antigens are duplicative for a particular type of disease. Accordingly, a person skilled in the art can discern from the data provided in the specification that detection of several particular cell surface marker antigens can be substituted with detection of other cell surface marker antigens to attain the same discriminatory image; thus, limiting the present claims to recite discrete subsets of antigens is inappropriate. Moreover, the power of the presently claimed method is the ability to use marker sets to create such images and not by using particular markers, which would not exclude others from picking a different set of seven cell surface marker antigens, as provided in the specification, to obtain the same result. As described in the specification and recited in the

instant claims, cell surface marker antigens that distinguish leukemias of T cell, B cell, or myeloid lineage can be readily determined by a person skilled in the art from the data and the list of forty-seven cell surface marker antigens provided in Table 4. Applicants respectfully submit that this genus is not large and is clearly characterized. Applicants should, therefore, be allowed to encompass the true scope and utility of their invention because every member of the genus that is set forth in the subset is adequately described and set forth in the present application.

Applicants therefore submit that the specification reasonably conveys to a person skilled in the art that applicants possessed the claimed invention at the time the Application was filed. Accordingly, Applicants respectfully submit that the Application complies with the written description requirement under 35 U.S.C. § 112, first paragraph, and respectfully request that the rejection be withdrawn.

REJECTIONS UNDER 35 U.S.C. § 103

In the Office Action dated February 4, 2005, claims 1, 2, and 18-20 are rejected under 35 U.S.C. § 103, allegedly for being obvious over Chang (U.S. Patent No. 4,591,570) in view of Terstappen (U.S. Patent No. 5,234,816). The Action also rejects claims 1, 2, and 18-20 for allegedly begin obvious over Chang in view of Verwer (U.S. Patent No. 5,605,805). The Action asserts that Chang teaches that antibodies which bind to cell surface markers may be bound to a solid support for determining whether certain cells will bind to these antibodies. While the Action concedes that Chang fails to teach a method for determining which antigens are expressed on leukemia cells, the Action asserts that Terstappen teaches the relevant antigens for discriminating among different types of leukemias. The Action thus alleges that a person having ordinary skill in the art would have found it obvious to alter the method of Chang to include antibodies that bind to CD antigens for classifying leukemias. The Action notes that the basis for these rejections is applicable to Chang in view of both Terstappen and Verwer (page 3, lines 5-6).

Applicants respectfully traverse this ground of rejection and submit that the amended claims meet the requirements for nonobviousness. To establish a *prima facie* case of obviousness the Action must show (1) that the references teach or suggest all claim limitations;

(2) that the references provide some teaching, suggestion, or motivation to combine or modify the teachings of the prior art to produce the claimed invention; and (3) that the combined teachings of the references indicate that by combining the references, a person having ordinary skill in the art will achieve the claimed invention with a reasonable expectation of success. When rejection of claims depends upon a combination of prior art references, something in the prior art as a whole must suggest the desirability, thus the obviousness, of making the combination (*see In re Rouffet*, 149 F.3d 1350, 1355, 47 U.S.P.Q.2d 1453 (Fed. Cir. 1998)).

Neither Chang alone, nor Chang in combination with either Terstappen or Verwer, teaches or suggests each and every limitation of the pending claims. Each of Chang, Terstappen, or Verwer fails to teach or suggest a method for identifying a leukemia of T cell, B cell, or myeloid lineage in a subject by contacting a biological sample comprising leukocytes from a subject with an array of immunoglobulin molecules that are immobilized to a solid surface and that are specific for cell surface marker antigens, wherein the cell surface marker antigens comprise at least seven cell surface marker antigens selected from the list in Table 4, and wherein the cell surface marker antigens distinguish leukemias of T cell, B cell, or myeloid lineage. Furthermore, none of the cited documents teaches a method for identifying a leukemia that is of T cell, B cell, or myeloid lineage by determining which cell surface marker antigens have bound to which immobilized immunoglobulin molecules to establish a differential pattern of density of binding that identifies a leukemia that is of T cell, B cell, or myeloid lineage.

Chang fails to teach, suggest, or motivate a person having ordinary skill in the art to combine its teachings with any other prior art teaching to obtain Applicants' presently claimed invention with a reasonable expectation of success. Chang merely teaches a general method for analyzing multiple antibody-antigen binding interactions and fails to provide any suggestion or motivation for using the method for identifying a leukemia that is of T cell, B cell, or myeloid lineage in a human subject. Chang also fails to teach or suggest that determining which cell surface marker antigens have bound to which immobilized immunoglobulin molecules establishes a *differential pattern of density of binding*. By contrast, Chang teaches that the "density of antibodies should be sufficient to yield, upon contact with an appropriate concentration of cells which have cell surface antigens that bind to the antibodies, a

microscopically *uniform layer of bound cells* covering the entire antibody-coated spot." (*See* Chang, column 3, lines 20-25; Figures 1 and 3; (emphasis added)).

Terstappen also fails to provide any teaching, suggestion, or motivation to combine or modify the teachings of the prior art to produce Applicants' claimed method. Terstappen teaches a method for classifying leukemias that uses different techniques and analyses and does not remotely suggest any desirability to combine the teachings therein with any other prior art to achieve Applicants' invention. Verwer teaches a method for classifying leukemias that also uses different techniques and analyses and does not suggest any desirability to combine the teachings therein with any other prior art to achieve Applicants' method for identifying a leukemia that is of a T cell, B cell, or myeloid lineage. Thus, the cited documents lack the requisite suggestion or motivation to combine the teachings therein to obtain Applicants' claimed method.

Applicants therefore respectfully submit that the claims meet the requirements for nonobviousness under 35 U.S.C. § 103 and request that this rejection be withdrawn.

In the Office Action dated February 4, 2005, claims 1, 2, 18, 19, and 21 are also rejected under 35 U.S.C. § 103, allegedly for being obvious over Hoeffler (U.S. Publication No. 2002/0164656) in view of Terstappen (U.S. Patent No. 5,234,816). The Action alleges that Hoeffler, as evidenced in claim 28 therein, contemplates using known antibodies for diagnosing a disorder comprising contacting an array of antibodies that are specific for one or more antigens characteristic of a disorder. The Action also alleges that the present claims encompass use of cell lysates as well as whole cells.

Applicants respectfully traverse this ground of rejection and submit that the amended claims meet the requirements for nonobviousness. Applicants respectfully submit neither Hoeffler alone, nor Hoeffler in combination with Terstappen, teaches or suggests each and every limitation of the pending claims. Each cited document alone or in combination fails to teach or suggest a method for identifying a leukemia in a subject that is of T cell, B cell, or myeloid lineage by contacting a biological sample comprising leukocytes from the subject with an array of immunoglobulin molecules that are immobilized to a solid surface and that are

specific for cell surface marker antigens, wherein the cell surface marker antigens comprise at least seven cell surface marker antigesn selected from the list in Table 4, and wherein the cell surface marker antigens distinguish leukemias of T cell, B cell, or myeloid lineage. Furthermore, neither document teaches a method for identifying a leukemia that is of T cell, B cell, or myeloid lineage, wherein a leukocyte associated with a leukemia of one lineage (*e.g.*, a T cell, B cell, or myeloid leukemia) is distinguishable from a leukocyte associated with a leukemia of a different lineage, by determining differential binding density of immunoglobulins to the cell surface marker antigens.

Hoeffler fails to teach a method that comprises immunoglobulins that are specific for CD antigens, which are cell surface antigens. Hoeffler also fails to teach or suggest contacting leukocytes in a biological sample with an array of immunoglobulin molecules that specifically bind cell surface marker antigens as recited, wherein the at least seven cell surface marker antigens distinguish leukemias of T cell, B cell, or myeloid lineage. Hoeffler is silent with regard to using a sample containing intact cells, such as leukocytes, in the methods taught therein. Hoeffler teaches that antigens used in the method described therein are often proteins, although the antigens may be organic chemical compounds, carbohydrates, nucleic acids, and that the antigens may be isolated or semi-isolated, whether recombinantly made or naturally occurring (Hoeffler, paragraph 42).

Terstappen fails to teach or suggest that a leukemia of T cell, B cell, or myeloid lineage may be identified by contacting leukocytes in a biological sample with an array of immunoglobulin molecules that are immobilized to a solid support, wherein binding of the immobilized immunoglobulin molecules to the leukocytes that express cell surface marker antigens establishes a differential pattern of density of binding. Terstappen fails to teach such a simultaneous analysis of each immunoglobulin/antigen binding interaction and instead teaches a sequential analysis of antibody pairings.

Furthermore, Hoeffler fails to suggest, teach, or motivate a person having ordinary skill in the art to combine its teachings with any other prior art teaching to obtain the claimed method for identifying a leukemia that is of T cell, B cell, or myeloid lineage with a reasonable expectation of success. Terstappen also fails to provide any teaching, suggestion, or

motivation to combine or modify the teachings of the prior art to produce Applicants' claimed method. Terstappen teaches a method for classifying leukemias that uses different techniques and analyses and does not remotely suggest any desirability to combine the teachings therein with any other prior art to achieve Applicants' invention.

Thus, a *prima facie* case of obviousness has not been established because the cited documents fail to teach or suggest, alone or in combination, each feature of the pending claims, and lack the requisite suggestion or motivation to combine the teachings therein to obtain Applicants' claimed method. Accordingly, Applicants respectfully submit that the pending claims satisfy the requirements for nonobviousness under 35 U.S.C. § 103 and request that these rejections be withdrawn.

Applicants respectfully submit that claims 1, 2, and 18-23 are allowable. Favorable consideration and a Notice of Allowance are earnestly solicited. In the event that the Examiner believes a teleconference will facilitate prosecution of this case, the Examiner is invited to telephone the undersigned at 206-622-4900.

Respectfully submitted,

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